in 1 mL of THF was added to the mixture at -78 °C, and the reaction mixture was stirred for 30 min at the same temperature. After being quenched with saturated aqueous NH_4Cl solution, the mixture was extracted with ether (10 mL × 3). The combined extracts were washed with saturated aqueous NaCl solution. The residue upon workup was chromatographed on silica gel (1 g) with *n*-hexane–ethyl acetate (1:3 v/v) to yield methoxymethyl ether **35** (37 mg, 83%) as a colorless oil: IR ($CHCl_3$) 3650–3400 (OH) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.05 (3 H, s, CH_3), 1.29 (3 H, s, CH_3), 3.38 (3 H, s, OCH_3), 3.65 (1 H, dd, J = 7.0 and 10.0 Hz, C_{21}-H_2), 3.76 (1 H, dd, J = 2.0 and 10.0 Hz, C_{21}-H_2), 3.90–4.00 (4 H, m, OCH_2CH_2O), 4.47 (1 H, br s, HOCH), 4.67 (2 H, s, OCH_2O), 5.29 (1 H, br s, CH=C); MS m/z 452 (M^+); exact mass calcd for $C_{25}H_{40}O_7$ 452.2774 (M^+), found 452.2782; $[\alpha]^{25}_D$ -38.20° (*c* 0.445, $CHCl_3$).

17α-Hydroxy-21-(methoxymethoxy)pregn-5-ene-3,11,20-trione 3-(Ethylene acetal) (36). To a stirred solution of DMSO (12 mg, 0.16 mmol) in 1 mL of CH_2Cl_2 was added oxalyl chloride (20 mg, 0.16 mmol) at -78 °C. After the mixture was stirred for 10 min at -78 °C, methoxymethyl ether **35** (21 mg, 0.046 mmol) was added to the mixture at the same temperature. After stirring was continued for 1 h at -78 °C, triethylamine (101 mg, 1 mmol) was added at the same temperature, and the reaction mixture was stirred for 1 h at 0 °C. The reaction mixture was then poured into 2 mL of 5% hydrochloric acid and extracted with chloroform (10 mL × 3). The combined extracts were washed with saturated aqueous NaCl solution. The residue upon workup was chromatographed on silica gel (500 mg) with *n*-hexane–ethyl acetate (1:1 v/v) to give diketone **36** (15 mg, 72%) as colorless needles: mp 181–182 °C (ether); IR ($CHCl_3$) 1725, 1705 (C=O) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.53 (3 H, s, CH_3), 1.21 (3 H, s, CH_3), 2.31 (1 H, dt, J = 8.0 and 11.0 Hz), 2.57 (1 H, dd, J = 2.0 and 15.0 Hz), 2.62 (1 H, dt, J = 3.0 and 14.0 Hz), 2.72–2.80 (2 H, m), 3.39 (3 H, s, OCH_3), 3.90–4.98 (4 H, m, OCH_2CH_2O), 4.28 (1 H, d, J = 17.0 Hz, OCH_2CO), 4.53 (1 H, d, J = 17.0 Hz, OCH_2CO), 4.66 (2 H, br s, OCH_2O), 5.35 (1 H, br s, CH=C); MS m/z 448 (M^+); exact mass calcd for $C_{25}H_{36}O_7$ 448.2461 (M^+), found 448.2474; $[\alpha]^{25}_D$ +284° (*c* 0.915, $CHCl_3$).

(+)-Cortisone (1). A solution of diketone **36** (60 mg, 0.13 mmol) in 0.5 mL of aqueous 10% hydrochloric acid solution and 5 mL of methanol was stirred at room temperature for 96 h. The mixture was basified with $NaHCO_3$ and the solvent was then evaporated. The residue was diluted with 5 mL of water and extracted with chloroform (10 mL × 3). The combined extracts were washed with saturated aqueous NaCl solution. The residue upon workup was chromatographed on silica gel (500 mg) with *n*-hexane–ethyl acetate (2:3 v/v) to afford cortisone (1) (36 mg, 75%) as colorless needles: mp 213–215 °C (ethanol) [authentic sample[17] mp 214–216 °C (ethanol)]; IR ($CHCl_3$) 3550–3300 (OH), 1710, 1670 (C=O) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.67 (3 H, s, CH_3), 1.40 (3 H, s, CH_3), 3.00 (1 H, br s), 4.27 (1 H, dd, J = 3.0 and 17.0 Hz, OCH_2CO), 4.65 (1 H, dd, J = 4.0 and 17.0 Hz, OCH_2CO), 5.71 (1 H, s, CH=CO); MS m/z 360 (M^+); $[\alpha]^{25}_D$ +190.38° (*c* 0.104, EtOH) [authentic sample[17] $[\alpha]^{25}_D$ +196.80° (*c* 0.188, EtOH)]. The spectra of this sample are superimposable upon those of the authentic sample.[17]

Cortisone 21-(*S*)-α-Methoxy-α-(trifluoromethyl)phenylacetate (37). To a stirred solution of cortisone (1) (5.2 mg, 0.011 mmol), triethylamine (7.8 mg, 0.077 mmol), and a catalytic amount of (dimethylamino)pyridine in 1 mL of CH_2Cl_2 was added dropwise (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (8.4 mg, 0.033 mmol) at room temperature. After stirring was continued for 1 h at the same temperature, the reaction mixture was diluted with 10 mL of CH_2Cl_2 and washed with aqueous 10% hydrochloric acid, saturated aqueous $NaHCO_3$, and NaCl solutions. The residue upon workup was chromatographed on silica gel (100 mg) with *n*-hexane–ethyl acetate (1:2 v/v) to give mono MTPA ester **37** (8.1 mg, 99%) as a colorless powder: IR ($CHCl_3$) 3550 (OH), 1760, 1740, 1710, 1670 (C=O) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.73 (3 H, s, CH_3), 1.42 (3 H, s, CH_3), 3.64 (3 H, s, OCH_3), 4.97, 5.10 (2 H, each d, J = 11.0 Hz, CH_2O), 5.75 (1 H, br s, CH=C), 7.41–7.45 (3 H, m, ArH), 7.62–7.66 (2 H, m, Ar H); MS m/z 576 (M^+); exact mass calcd for $C_{31}H_{35}O_7F_3$ 576.2336 (M^+), found 576.2349. This derivative was identical in all aspects with the sample that was prepared from authentic cortisone.[17]

Registry No. **1**, 53-06-5; **6**, 113627-43-3; **7**, 79618-03-4; **8** (isomer 1), 128802-39-1; **8** (isomer 2), 128898-72-6; **8** (isomer 3), 128898-73-7; **8** (isomer 4), 128898-74-8; **9** (isomer 1), 128802-40-4; **9** (isomer 2), 128898-75-9; **10** (isomer 1), 128802-41-5; **10** (isomer 2), 128898-76-0; **11**, 128802-42-6; **12**, 128802-43-7; **13**, 128802-44-8; **14**, 887-47-8; **15**, 128802-45-9; **16**, 128802-46-0; **17**, 128802-47-1; **18**, 128802-48-2; **19**, 128802-49-3; α-**20**, 128802-50-6; β-**20**, 128802-51-7; **21**, 128802-52-8; **22**, 128802-53-9; **23**, 128802-54-0; **24**, 128802-55-1; **25**, 3597-44-2; **26**, 3941-62-6; **27**, 3941-63-7; **28**, 128802-56-2; **29**, 128802-57-3; **30**, 128802-58-4; **31**, 128802-59-5; **32**, 128802-60-8; **34**, 128802-61-9; **35**, 128822-25-3; **36**, 128802-62-0; **37**, 128802-63-1; MTPACE, 39637-99-5; CH_2=$C(CH_3)MgBN$, 13291-18-4; CH_3OCH_2Cl, 107-30-2; $(CH_3O)_2C(CH_3)_2$, 77-76-9; CH_2N_2, 334-88-3; $BrCH_2CH$=$C(Cl)CH_3$, 51430-83-2; $HOCH_2CH_2OH$, 107-21-1; $(C_4H_9)_3SnCH_2OCH_2OCH_3$, 100045-83-8.

Supplementary Material Available: NMR spectra for 19 compounds (19 pages). Ordering information is given on any current masthead page.

Synthesis of the Ziegler Key Intermediate and Related Precursors for the Synthesis of Forskolin and Erigerol

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The Ziegler key intermediate **2**, previously used in three total syntheses of forskolin (**1**), has been synthesized from enone **5a**. Starting from **5a**, two sequences to **2** have been developed (Schemes I and II). The key step in both sequences is the early and stereoselective introduction of the C-6, C-7 oxygen functional groups present in the natural product. This constitutes a new formal total synthesis of forskolin. The preparation of the key intermediate **18**, a diastereomer of **2**, potentially useful for the synthesis of analogues of **1** and for the synthesis of the highly oxygenated labdane diterpene erigerol (**3**), starting also from **5a**, is described.

Forskolin (**1**), the highly oxygenated labdane diterpene isolated from the roots of the Indian herb *Coleous forskolii*,[1] has generated an enormous amount of synthetic interest[2-6] because of its unique structural features and its

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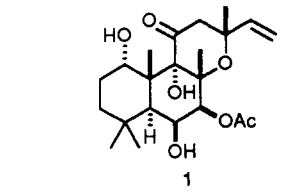
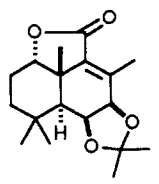
broad range of physiological activities.[7] Recently, three different routes culminated in the total syntheses of this highly challenging target,[8] all of which, proceed through the intermediacy of lactone **2**, first synthesized by Ziegler et al.[2a]

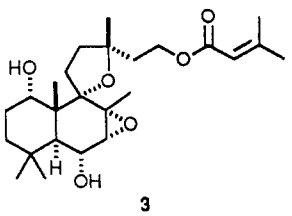
The related diterpene erigerol (**3**),[9] isolated in very small amounts from the aerial parts of *Erigeron philadelphicus* and with a structural complexity comparable to that of **1**, has also received attention from a synthetic point of view. The partial synthesis of **4**,[10] a closely related derivative of the natural product (**3**), and the total synthesis of erigerol[11] have already been reported. Probably due to the lack of material, the physiological activities of **3** are still unknown; however, the arrangement of oxygenated functional groups on the ring system may have biological implications.



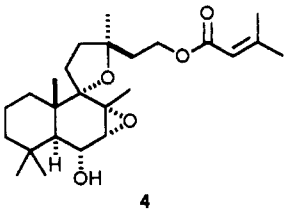
1



2

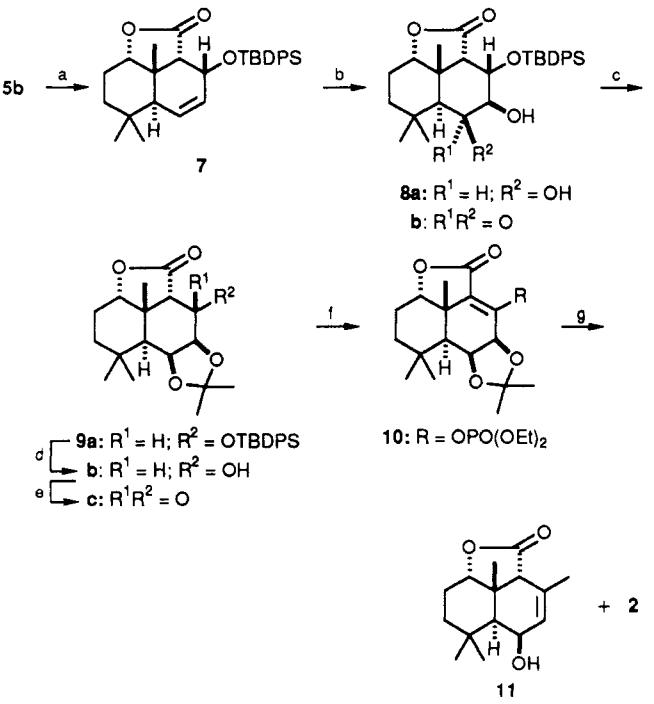


3



4

Scheme I[a]



[a] Reagents and conditions: (a) (t-Bu)Ph_2SiCl, imidazole, DMF, 20 °C, 4 h; (b) OsO_4, py, 20 °C, 24 h, $NaHSO_3$, py, H_2O, 20 °C, 1 h; (c) $Me_2C(OMe)_2$, TsOH catalyst, 20 °C, 24 h; (d) *n*-Bu_4NF, THF, 20 °C, 48 h; (e) Jones reagent, acetone, 0–20 °C, 1 h; (f) $ClPO(OEt)_2$, NaH, THF, 0 °C, 30 min, 20 °C, 2 h; (g) $LiMe_2Cu$, Et_2O, −78 °C, 3 h, −23 °C, 4 h.

Having recently developed a simple methodology for the preparation of tricyclic enone **5a** and other intermediates for the synthesis of forskolin (**1**),[2b] we sought to further demonstrate the utility of this polyfunctionalized starting material for the synthesis of the Ziegler key intermediate (**2**)[12] and, furthermore, for the preparation of substrates potentially useful for the stereoselective synthesis of erigerol (**3**).

Our initial plan for the synthesis of **2** was to use the known pseudoequatorial alcohol **5b** as starting material. We envisioned that by using a bulky hydroxyl protecting group, the double bond could be stereoselectively hydroxylated from the β-face, allowing the introduction of the *cis*-diol unit at C-6 and C-7 with the desired stereochemistry at an early stage of the sequence. Protection of the diol moiety and selective deprotection of the alcoholic function at C-8 followed by oxidation would then furnish a β-keto lactone, adequately substituted, to serve as precursor of **2**. In fact, completion of the synthesis would require only the conversion of the keto group into the vinylic methyl moiety present in **2**. The methodology described by Weiler et al. could be an excellent alternative for such a conversion.[13]

Since the reduction of enone **5a** under standard conditions (sodium borohydride, cerium(III) chloride, methanol, room temperature) led to a 2:1 mixture of allylic alcohols **5b** and **5c** in good yield,[2b] we decided to study this reduction again, in order to improve the availability of the proposed starting material **5b**. After considerable experimentation, we found that the slow addition of sodium borohydride in ethanol to a dichloromethane–ethanol so-

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(2) Preparation of AB ring system: (a) Ziegler, F. E.; Jaynes, B. H.; Saindane, M. T. *Tetrahedron Lett.* **1985**, *26*, 3307. (b) Somoza, C.; Darias, J.; Rúveda, E. A. *J. Org. Chem.* **1989**, *54*, 1539. (c) Nicolaou, K. C.; Kubota, S.; Li, W. S. *J. Chem. Soc., Chem. Commun.* **1989**, 512. (d) Venkataram, H.; Cha, J. K. *J. Org. Chem.* **1989**, *54*, 2505. (e) Kanematsu, K.; Nagashima, S. *J. Chem. Soc., Chem. Commun.* **1989**, 1028. (f) Baraldi, P. G.; Barco, A.; Beneti, S.; Ferretti, V.; Pollini, G. P.; Polo, E.; Zanirato, V. *Tetrahedron* **1989**, *45*, 1517. (g) Mukhopadhyay, A.; Ali, S. M.; Husain, M.; Suryawanshi, S. N.; Bhakuni, D. S. *Tetrahedron Lett.* **1989**, *30*, 1853. (h) Begley, M. J.; Cheshire, D. R.; Harrison, T.; Hutchinson, J. H.; Myers, P. L.; Pattenden, G. *Tetrahedron* **1989**, *45*, 5215. (i) Leclaire, M.; Lallemand, J. Y. *Tetrahedron Lett.* **1989**, *30*, 6331. (j) Trost, B. M.; Holcomb, R. C. *Ibid.* **1989**, *30*, 7157. For further synthetic approaches to the AB ring system prior to 1988, see the cited references in ref 2b.

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(4) Preparation of ring C: Ziegler, F. E.; Jaynes, B. H. *Tetrahedron Lett.* **1988**, *29*, 2031 and references cited therein.

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(6) Chemical modifications on forskolin and synthesis of some of its analogues: (a) Hrib, N. J. *J. Chem. Soc., Chem. Commun.* **1987**, *1338*. (b) Scherkenbeck, J.; Bottger, D.; Welzel, P. *Tetrahedron* **1987**, *43*, 3797. (c) Vishwakarma, R. A. *Tetrahedron Lett.* **1989**, *30*, 131. (d) Delpech, B.; Lett, R. *Ibid.* **1989**, *30*, 1521. (e) Shutske, G. M. *J. Chem. Soc., Perkin Trans. 1*, **1989**, 1544. (f) Kosley, R. W., Jr.; Cherill, R. J. *J. Org. Chem.* **1989**, *54*, 2972. (g) O'Malley, G. J.; Spahl, B.; Cherill, R. J.; Kosley, R. W., Jr.; *Ibid.* **1990**, *55*, 1102.

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(9) Waddell, T. G.; Osborne, C. B.; Collison, R.; Levine, M. J.; Cross, M. C.; Silverton, J. V.; Fales, H. M.; Sokoloski, E. A. *J. Org. Chem.* **1983**, *48*, 4450.

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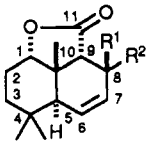
(11) Kienzle, F.; Stadlwieser, J.; Rank, W.; Mergelsberg, I. *Tetrahedron Lett.* **1988**, *29*, 6479.

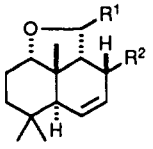
(12) A part of this work has been published in a preliminary form: Colombo, M. I.; Somoza, C.; Zinczuk, J.; Bacigaluppo, J. A.; Rúveda, E. A. *Tetrahedron Lett.* **1990**, *31*, 39.

(13) Sum, F.-W.; Weiler, L. *Can. J. Chem.* **1979**, *57*, 1431.

lution of **5a**, in the presence of cerium(III) chloride at −78 °C, afforded exclusively **5b** in 78% yield. When an excess of sodium borohydride was used, the lactone moiety of **5a** was also reduced, giving hemiacetal **6a** as a mixture of epimers at C-11. Exposure of this mixture to a catalytic amount of *p*-toluenesulfonic acid in methanol gave rise to the methyl acetal **6b** as a single anomer in good overall yield.



5a: R^1R^2 = O
b: R^1 = H; R^2 = OH
c: R^1 = OH; R^2 = H



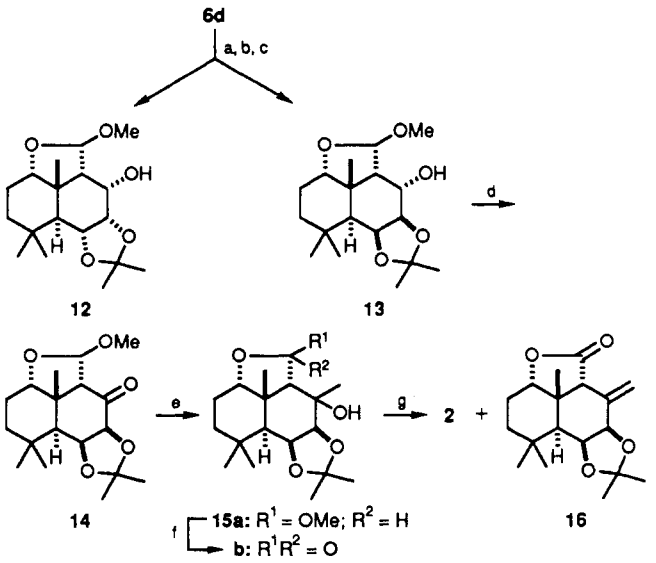
6a: R^1 = OH; R^2 = OH
b: R^1 = OMe; R^2 = OH
c: R^1 = OMe; R^2 = OTBDPS
d: R^1 = OMe; R^2 = OAc

As outlined in Scheme I, protection of the hydroxyl group of **5b** as *tert*-butyldiphenylsilyl ether (**5b** → **7**) followed by hydroxylation with osmium tetraoxide under stoichiometric conditions led, in good yield, to an isomerically pure diol, whose ^{1}H NMR spectrum showed signals at δ 3.68 (dd, J = 3.4 and 9.7 Hz) and 4.32 (dd, J = 1.2 and 3.4 Hz) attributed to H-6 and H-7 and indicating the presence of the 6β,7β-diol moiety of **8a**. Attempted hydroxylation of **7** with osmium tetraoxide under catalytic conditions was unsuccessful; **7** either reacted very slowly (*N*-methylmorpholine *N*-oxide, aqueous *tert*-butyl alcohol, room temperature)[14] or tended to give products of overoxidation such as α-hydroxy ketone **8b**[15] (trimethylamine *N*-oxide, aqueous *tert*-butyl alcohol under reflux).[16]

Treatment of the diol **8a** with 2,2-dimethoxypropane in the presence of *p*-toluenesulfonic acid led quantitatively to the acetonide **9a**. Fluoride-induced desilylation of **9a** followed by oxidation of the corresponding alcohol **9b** with Jones reagent, afforded the β-keto lactone **9c**. With access to **9c** secure, we focused on the conversion of the keto group into the vinylic methyl moiety present in **2**. Toward this end, **9c** was smoothly converted into the enol phosphate **10** by treatment with sodium hydride and diethyl phosphorochloridate.[13] Unfortunately, the conversion of **10** into **2** in acceptable yields was more difficult than expected. After considerable experimentation, however, we found that the treatment of **10** with lithium dimethylcuprate at −78 °C for 3 h followed by stirring at −23 °C for 4 h afforded **2** in low yield and together with an appreciable amount of **11**. Apparently, **2** suffers an easy lithium dimethylcuprate induced reductive cleavage of its γ-oxygen with migration of the double bond giving **11**.[17] Interestingly enough, **11**, prepared by several synthetic sequences, has been transformed into **2**.[2a,d,8c]

In view of the foregoing results we decided to explore a more efficient sequence toward **2**, from the readily available methyl acetal **6b**. As in the case of **5b**, we assumed that by using a bulkyl hydroxyl protecting group at C-8, the double bond of **6b** could be also stereoselectively hydroxylated from the β-face of the molecule. As expected, hydroxylation of **6c** with osmium tetraoxide under stoichiometric conditions afforded the desired diastereoisomeric product as the major component in a 3:1 mixture of diols (^{1}H NMR).[18] The effect of other hydroxyl protecting groups was investigated further, in particular because of the report that, at least in simple cyclic systems, osmium tetraoxide approaches preferentially to the face of the olefinic bond opposite to that of a preexisting acyloxy group.[19] By stoichiometric osmylation of acetate **6d**, the desired β-diol was again the major component in a mixture with the same ratio of diastereomers as the one obtained with **6c**, based on the ^{1}H NMR spectrum of the crude reaction product. With this stereoselective hydroxylation procedure suitable for preparative purposes, we turned our attention to more advanced steps of the sequence (Scheme II). Without separation, the diols were transformed into their corresponding isopropylidene derivatives by treatment of the mixture with 2,2-dimethoxypropane in the presence of a catalytic amount of *p*-toluenesulfonic acid. The alcohols (**12** and **13**) obtained by basic hydrolysis of the acetoxy groups were then separated by chromatography on silica gel, and the major isomer **13** was oxidized with pyridinium dichromate to the ketone **14** in quantitative yield. At this point, the remaining steps to complete the synthesis of **2** were only the introduction of the C-8 methyl group and the conversion of the acetal group into the lactone moiety. Thus, reaction of **14** with an excess of methylmagnesium iodide gave a single tertiary alcohol (**15a**),[20] which, without further purification, was transformed into lactone **15b** by oxidation

Scheme II[a]



[a] Reagents and conditions: (a) OsO_4, py, 0 °C, 1 h, 20 °C, 12 h, $NaHSO_3$, THF, H_2O, 20 °C, 4 h; (b) $Me_2C(OMe)_2$, TsOH catalyst, 20 °C, 12 h; (c) K_2CO_3, MeOH, 20 °C, 12 h; (d) PDC, CH_2Cl_2, 20 °C, 4 h; (e) MeMgI, Et_2O, 0–20 °C, 1 h; (f) Jones reagent, acetone, 0–20 °C, 1 h; (g) $SOCl_2$, py, 0 °C, 1 h.

(14) Van Rheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *1973*.

(15) **8b**: mp 161–163 °C; IR ν 3500, 1780, 1735, 1430, 1160, 1120, 1100, 1080, 950, 860 cm^{-1}; ^{1}H NMR ($CDCl_3$ + D_2O) δ 7.74 (4 H, m), 7.40 (6 H, m), 4.37 (1 H, d, J = 8.8 Hz, H-7), 3.90 (1 H, t, H-1), 3.73 (1 H, dd, J = 6.7 and 8.8 Hz, H-8), 2.29 (1 H, br s, H-5), 2.00 (1 H, d, J = 6.7 Hz, H-9), 1.13 (9 H, s), 1.11 (3 H, s), 0.95 (3 H, s), 0.68 (3 H, s); ^{13}C NMR δ 206.36 (C-6), 172.52 (C-11), 136.12, 136.01, 133.90, 132.68, 129.78, 129.62, 127.60, 127.33 (Ph), 79.90 (C-1), 79.68 (C-7), 74.44 (C-8), 55.94 (C-9), 54.46 (C-5), 43.71 (C-10), 34.93 (C-3), 31.05 (4α-Me), 30.56 (C-4), 26.74 (4β-Me, CMe_3), 20.63 (C-2), 19.21 (C-Me_3), 17.19 (10-Me); found for (M^+ − Me) m/e 491.2240 ($C_{28}H_{32}O_5Si$ requires m/e 491.2254).

(16) Ray, R.; Matteson, D. S. *Tetrahedron Lett.* **1980**, *21*, 449.

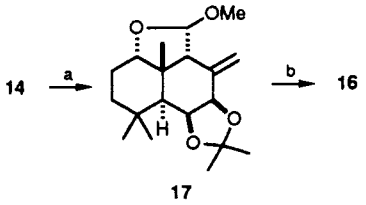
(17) For related transformations, see: (a) Ibuka, T.; Namg Chu, G.; Yoneda, F. *Tetrahedron Lett.* **1984**, *25*, 3247. (b) Corey, E. J.; Boaz, N. W. *Ibid.* **1985**, *26*, 6015.

(18) The ratio of both compounds was estimated by comparing the areas under the signals at δ 5.05 and 5.33, assigned to H-11 in each diastereomer.

(19) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron* **1984**, *40*, 2247.

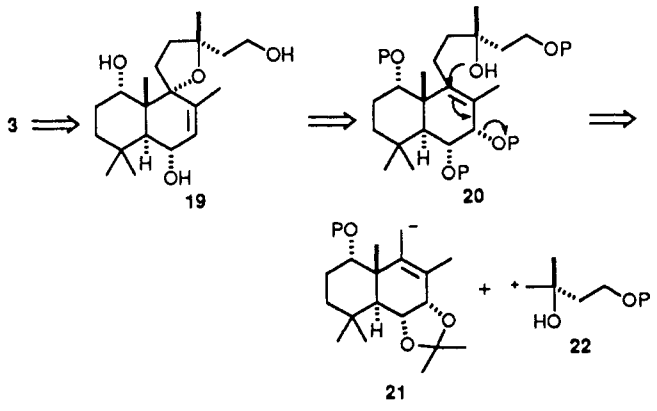
(20) In our preliminary report[12] we suggested, on the basis of related transformations, that the addition of methylmagnesium iodide ocurred from the β-face of ketone **14**, giving a tertiary alcohol with the hydroxyl group equatorial. However, a NMR analysis is being carried out in order to establish unambiguously the stereochemistry of **15a** and **24a**. These results will be published in due course.

Scheme III[a]



[a] Reagents and conditions: (a) $Ph_3P{=}CH_2$, THF, 20 °C, 3 h; (b) Jones reagent, acetone, 0–20 °C, 7 h.

Scheme IV

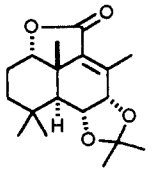


with Jones reagent in good overall yield.

Although the addition of methyllithium to **14** afforded also **15a** in lower yield than the Grignard reagent, both reagents favored the product of attack from the same face of the starting ketone.

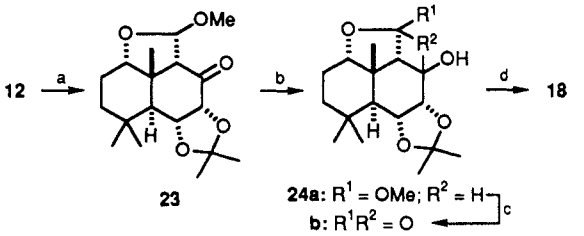
Finally, dehydration of **15a** with thionyl chloride in pyridine at 0 °C furnished a 10:1 mixture of **2** and the unconjugated isomer **16**, based on the ^1H NMR spectrum of the reaction product. Pure **2** obtained by slow crystallization of the crude product from diisopropyl ether was found to exhibit melting point, IR, ^1H, ^{13}C NMR, and mass spectra coincident with those previously reported.[2a,8b] As **16** has efficiently been converted into **2**,[2a,8b] its formation does not represent any disadvantage. On the contrary, we considered that the preparation of **16** starting with **14** might be useful as an alternative route to **2**. As outlined in Scheme III, Wittig methylenation of **14** yielded olefin **17** in reasonable yield; however, when **17** was oxidized with Jones reagent, under the same conditions as described above for **15a**, **16** was obtained in low yield together with an appreciable amount of unreacted starting material. As described in Scheme II, the synthesis of the Ziegler intermediate **2** was now completed. This constitutes a new formal total synthesis of forskolin (**1**).

As a corollary of our investigations toward forskolin (**1**), we also evaluated the use of the available minor alcohol **12** as starting material for the preparation of **18**. This



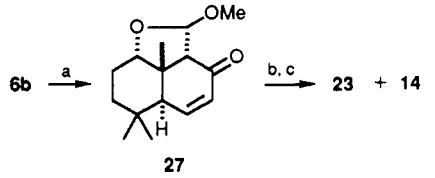
lactone acetonide could be a useful intermediate for the synthesis of analogues of **1** and also, for the total synthesis of erigerol (**3**). In fact, **18** could be considered the synthetic equivalent of synthon **21**, on the basis of the retrosynthetic analysis of **3**, as depicted in Scheme IV, and according to our own experience on the synthesis of the related product **4**.[10]

Scheme V[a]



[a] Reagents and conditions: (a) PDC, CH_2Cl_2, 20 °C, 31 h; (b) MeLi, Et_2O, 0 °C, 15 min; (c) Jones reagent, acetone, 0–20 °C, 45 min; (d) KOH, dioxane, 85 °C, 8 h.

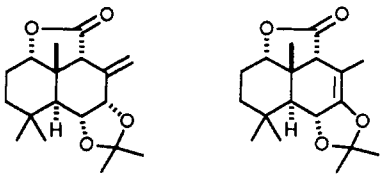
Scheme VI[a]



[a] Reagents and conditions: (a) PDC, CH_2Cl_2, 20 °C, 4 h; (b) OsO_4, py, 0 °C, 1 h, 20 °C, 6 h, $NaHSO_3$, THF, H_2O, 20 °C, 19 h; (c) $Me_2C(OMe)_2$, TsOH catalyst, 20 °C, 16 h.

In practice (Scheme V), oxidation of **12** with pyridinium dichromate afforded **23** in almost quantitative yield. However, in clear contrast with **14**, the addition of methylmagnesium iodide to **23** afforded a mixture of products from which a tertiary alcohol was isolated in low yield by column chromatography. On the other hand, treatment of **23** with an excess of methyllithium in ether at 0 °C furnished the same tertiary alcohol **24a**,[20] in good yield.

Completion of the synthesis of **18** required only oxidation of the acetal moiety of **24a** and dehydration of the resulting lactone alcohol. By oxidation with Jones reagent, **24a** was smoothly converted into **24b**. Unfortunately, thionyl chloride induced dehydration of **24b** gave a 3:1:5 mixture of **18** and the unconjugated isomers **25** and **26**,[21] respectively. After considerable experimentation, however, we found that the treatment of **24b** with solid potassium hydroxide in dioxane at 85–90 °C[22] for approximately 8 h afforded exclusively **18** in good yield.



In order to have a more direct sequence toward **18**, we considered it worthwhile to improve the availability of **23**. Thus, the hydroxylation reaction of enone **27** was investigated in the hope that osmium tetraoxide would ap-

(21) **26**: mp 108–111 °C; IR ν 1770, 1730, 1470, 1455, 1390, 1300, 1225 cm^{-1}; ^1H NMR δ 4.38 (1 H, br d, J = 10.0 Hz, H-6), 4.13 (1 H, t, J = 4.0 Hz, H-1), 2.61 (1 H, br s, H-9), 1.87 (3 H, br s, 8-Me), 1.46 (6 H, s), 1.25 (3 H, s), 1.06 (6 H, s); ^{13}C NMR δ 175.46 (C-11), 147.72 (C-7), 111.05 (OCO), 94.71 (C-8), 82.17 (C-1), 72.21 (C-6), 56.47 (C-9), 46.70 (C-5), 43.25 (C-10), 34.30 (C-3), 32.42 (Me), 31.83 (C-4), 27.24 (Me), 24.76 (Me), 22.19 (C-2), 21.96 (Me), 19.44 (Me), 12.83 (Me); mass spectrum, m/e (relative intensity) 306 (M^+, 14), 189 (32), 43 (100). Molecular mechanics calculations comparing the ground-state energy of structures **18** and **26** show the product **18** to be more stable, suggesting that, under these experimental conditions, **26** is the kinetic product of the reaction.

(22) Ziegler, F. E.; Jaynes, B. H. *Tetrahedron Lett.* **1985**, *26*, 5875.

proach preferentially from the less hindered α-face, allowing the introduction of the *cis*-diol unit with the desired stereochemistry. As outlined in Scheme VI, **6b** was smoothly oxidized with pyridinium dichromate to **27**. Osmylation of **27** under stoichiometric conditions afforded a mixture of diols which were transformed, without separation, into their corresponding acetonides. As anticipated, chromatographic separation of the mixture afforded pure **23** and a small amount of **14**.

In conclusion, the sequences described in this report, apart from providing simple and efficient access to key precursors for the synthesis of complex natural products such as forskolin (**1**) and erigerol (**3**), show the versatility of our tricyclic enone **5a**, as a starting material for the construction of highly functionalized molecules.

Experimental Section

Melting points were determined on a hot-stage microscope and are uncorrected. IR spectra were measured as solids in KBr disks, unless otherwise stated. NMR spectra were recorded at 80 MHz in $CDCl_3$ solutions, unless otherwise stated. The ^{13}C NMR spectra were measured at 20.15 MHz. The carbon chemical shifts were assigned by comparison with the reported data for related products and analysis of the generated CH/CH_3 and CH_2 subspectra (DEPT). Reactions were routinely run under a dry nitrogen atmosphere with magnetic stirring. Column chromatography was performed on silica gel 60 H, slurry packed, run under low pressure of nitrogen and employing increasing amounts of EtOAc in hexane as solvent. Analytical thin-layer chromatography (TLC) was conducted on Merck aluminum plates precoated with 0.2 mm of silica gel 60F-254. The homogeneity of all intermediates prior to the high-resolution mass spectral determinations was carefully verified by TLC.

The numbering sequence used for reporting NMR parameters is illustrated in structure **5**.

(2aβ,3α,5aα,8aβ,8bβ)-2a,3,5a,6,7,8,8a,8b-Octahydro-3-hydroxy-6,6,8b-trimethyl-2*H*-naphtho[1,8-*bc*]furan-2-one (5b). Cerium(III) chloride heptahydrate (317.4 mg, 0.85 mmol) was added to a solution of enone **5a** (200 mg, 0.86 mmol) in CH_2Cl_2 (7.4 mL) and absolute EtOH (7.4 mL) at room temperature. The solution was cooled to −78 °C, and $NaBH_4$ (16.28 mg, 0.43 mmol) in EtOH (4 mL) was added via syringe over 1.5 h. After being stirred for 2 h, the solution was warmed to −20 °C and quenched by the careful addition of pH 7 phosphate buffer (20 mL). The mixture was extracted with Et_2O (3 × 20 mL) and EtOAc (2 × 15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The residue was chromatographed to give pure **5b** (156 mg, 78%), mp 149–150 °C (lit.[2b] 149.5–150 °C); IR and ^1H NMR spectra coincident with those reported in ref 2b.

(2a,β,3α,5aα,8aβ,8bβ)-2a,3,5a,6,7,8,8a,8b-Octahydro-3-hydroxy-2-methoxy-6,6,8b-trimethyl-2*H*-naphtho[1,8-*bc*]-furan (6b). Via the same procedure as in preparing **5b**, the treatment of **5a** (500 mg, 2.14 mmol) and cerium(III) chloride heptahydrate (632 mg, 1.69 mmol) in a CH_2Cl_2 (32 mL) and absolute EtOH (32 mL) solution with $NaBH_4$ (180 mg, 4.76 mmol) in EtOH (32 mL) afforded **6a** (500 mg) as an epimeric mixture of hemiacetals on the basis of its ^1H NMR spectrum, with signals at δ 5.85 (3 H, m), 4.61 (1 H, m), 4.12 (0.7 H, t), 3.77 (0.3 H, t), 1.07 (s), 1.03 (s), 0.98 (s), 0.94 (s), 0.91 (s), 0.88 (s). This material was used in the next step without further purification.

To a stirred solution of crude **6a** (500 mg) in anhydrous MeOH (13 mL) was added a crystal of *p*-TsOH at room temperature. After 4 h, the reaction mixture was poured into brine (58 mL) and extracted with Et_2O (3 × 20 mL) and EtOAc (2 × 15 mL). The combined organic extracts were washed with saturated $NaHCO_3$ solution and brine, dried (Na_2SO_4), and evaporated. This residue (530 mg) may be used in the next step without further purification. A small sample was chromatographed, affording pure **6b**: mp 89–90 °C (diisopropyl ether); IR ν 3410, 3360, 1385, 1120, 975 cm^{-1}; ^1H NMR δ 6.03 (1 H, dd, J = 3.0 and 10.0 Hz, H-6), 5.80 (1 H, m, H-7), 5.31 (1 H, d, J = 6.15 Hz, H-11), 4.61 (1 H, ddd, J = 2.0, 4.0, 9.0 Hz, H-8), 4.01 (1 H, t, J = 3.2 Hz, H-1), 3.46 (3 H, s, OCH_3), 2.28 (1 H, d, J = 3.0 Hz, H-5), 2.20 (1 H, dd, J = 6.15 and 9.0 Hz, H-9), 1.02 (3 H, s), 0.95 (3 H, s), 0.88 (3 H, s); ^{13}C NMR δ 130.72 (C-6),* 128.09 (C-7),* 106.06 (C-11), 82.39 (C-1), 63.98 (C-8), 59.90 (C-9), 55.62 (OCH_3), 48.95 (C-10), 42.38 (C-5), 34.63 (C-3), 31.30 (4α-Me), 30.97 (C-4), 21.81 (C-2), 21.20 (4β-Me), 18.15 (10-Me) (the assignments for signals marked with an asterisk (*) may be reversed); mass spectrum, m/e (relative intensity) 220 (M^+ − 32, 1), 159 (100). Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.44; H, 9.54.

(3aβ,5aβ,6α,6aα,9aα,9bβ,9cβ)-Decahydro-6-hydroxy-1,1,8,8,9c-pentamethyl-5*H*-furo[4′,3′,2′:4,5]naphtho[1,2-*d*]-[1,3]dioxol-5-one (9b). To a stirred solution of alcohol **5b** (183 mg, 0.78 mmol) and imidazole (115 mg, 1.69 mmol) in anhydrous DMF (1 mL) was added *tert*-butyldiphenylsilyl chloride (0.22 mL, 0.85 mmol). After 4 h of stirring at room temperature, the mixture was poured into H_2O (5 mL) and extracted with $CHCl_3$ (3 × 5 mL). The combined organic extracts were washed with dilute HCl and brine, dried (Na_2SO_4), and evaporated. The residue was chromatographed to give essentially pure **7**: ^1H NMR δ 7.74 (4 H, m), 7.40 (6 H, m), 5.93 (1 H, dd, J = 3.6 and 9.4 Hz, H-6), 5.47 (1 H, ddd, J = 3.2, 4.8, and 9.4 Hz, H-7), 4.66 (1 H, ddd, J = 1.0, 4.8, and 7.2 Hz, H-8), 4.10 (1 H, t, J = 6.0 Hz, H-1), 2.70 (1 H, br dd, J = 3.2 and 3.6 Hz, H-5), 2.33 (1 H, d, J = 7.2 Hz, H-9), 1.07 (9 H, s), 1.03 (3 H, s), 0.98 (3 H, s), 0.94 (3 H, s). This material was used in the next step without further purification. osmium tetraoxide (217 mg, 0.85 mmol) was added to a stirred solution of **7** in pyridine (2 mL) at room temperature. After 24 h of stirring in the dark, the osmate ester was reduced by adding pyridine (5.5 mL), H_2O (8 mL), and solid $NaHSO_3$ (500 mg). The mixture was stirred vigorously at room temperature for 1 h, after which it was poured into H_2O (10 mL) and extracted with $CHCl_3$ (3 × 10 mL). The combined organic extracts were washed with H_2O (2 × 5 mL), 5% aqueous HCl (4 × 5 mL), and brine (2 × 5 mL), dried (Na_2SO_4), and evaporated. The residue was chromatographed to give pure **8a** (353 mg, 90% from **5b**) as a solid: mp 171–171.5 °C; IR ν 3510, 3430, 1775, 1470, 1430, 1395, 1370, 1270 cm^{-1}; ^1H NMR ($CDCl_3$ + D_2O) δ 7.77 (4 H, m), 7.40 (6 H, m), 4.32 (1 H, dd, J = 1.2 and 3.4 Hz, H-6), 4.14 (1 H, dd, J = 5.7 and 9.7 Hz, H-8), 3.75 (1 H, t, J = 3.4 Hz, H-1), 3.68 (1 H, dd, J = 3.4 and 9.7 Hz, H-7), 2.05 (1 H, d, J = 5.7 Hz, H-9), 1.13 (9 H, s), 1.08 (3 H, s), 1.06 (3 H, s), 0.93 (3 H, s); ^{13}C NMR δ 174.15 (C-11), 135.90, 135.66, 133.35, 129.87, 127.78, 127.67 (Ph), 83.01 (C-1), 74.54 (C-8), 69.71 (C-6),* 68.69 (C-7),* 56.47 (C-9), 45.42 (C-5), 43.82 (C-10), 36.10 (C-3), 32.51 (C-4), 31.49 (4α-Me), 26.88 (CMe_3), 22.59 (4β-Me), 21.25 (C-2), 19.96 (10-Me), 19.26 (CMe_3) (the assignments for signals marked with an asterisk (*) may be reversed); mass spectrum, m/e (relative intensity) 452 (M^+ − 56, 4), 199 (100).

To a stirred solution of **8a** (320 mg, 0.63 mmol) in 2,2-dimethoxypropane (2 mL) was added a crystal of *p*-TsOH at room temperature. After 24 h, the reaction mixture was diluted with CH_2Cl_2 (10 mL), washed with H_2O (2 × 3 mL) and brine (5mL), dried (Na_2SO_4), and evaporated to afford essentially pure **9a** (335 mg, 97%): IR ν 1770, 1600, 1460, 1430, 1380, 1250, 1210 cm^{-1}; ^1H NMR δ 7.77 (4 H, m), 7.40 (6 H, m), 4.39 (1 H, dd, J = 2.2 and 6.7 Hz, H-6), 4.32 (1 H, dd, J = 5.1 and 5.7 Hz, H-8), 4.08 (1 H, dd, J = 5.1 and 6.7 Hz, H-7), 3.90 (1 H, dd, J = 5.6 and 6.4 Hz, H-1), 2.32 (1 H, d, J = 5.7 Hz, H-9), 1.95 (1 H, d, J = 2.2 Hz, H-5), 1.25 (6 H, s), 1.12 (3 H, s), 1.08 (9 H, s), 1.06 (6 H, s).

A solution of **9a** (300 mg, 0.55 mmol) in a 1 M solution of tetra-*n*-butylammonium fluoride (1 mL) was stirred at room temperature for 48 h. After removal of the solvent, the residue was chromatographed to give **9b** (166 mg, 98%) as a solid: mp 143.5–144 °C (EtOAc); IR ν 3420, 1750, 1210 cm^{-1}; ^1H NMR δ 4.57 (1 H, dd, 2.2 and 5.0 Hz, H-6), 4.18 (1 H, t, J = 4.0 Hz, H-1), 4.04 (2 H, m, H-7, H-8), 2.74 (1 H, d, J = 6.5 Hz, H-9), 1.45 (1 H, br s, H-5), 1.52 (3 H, s), 1.50 (3 H, s), 1.36 (3 H, s), 1.13 (3 H, s), 1.05 (3 H, s); ^{13}C NMR δ 177.69 (C-11), 110.33 (OCO), 85.32 (C-1), 80.59 (C-6),* 73.48 (C-7),* 68.91 (C-8), 55.64 (C-9), 42.37 (C-5), 42.20 (C-10), 35.59 (C-3), 32.45 (4α-Me), 31.18 (C-4), 27.83 (Me, acetonide), 25.35 (Me, acetonide), 23.25 (4β-Me), 21.55 (C-2), 20.52 (10-Me) (the assignments for signals marked with an asterisk (*) may be reversed); mass spectrum, m/e (relative intensity) 310 (M^+, 2), 295 (73), 240 (52), 191 (47), 189 (48), 43 (100); found for M^+ m/e 310.1785 ($C_{17}H_{26}O_5$ requires m/e 310.1780).

(3aβ,6aα,9aα,9bα,9cβ)-1,2,3,3a,6a,9a,9b,9c-Octahydro-1,1,6,8,8,9c-hexamethyl-5*H*-furo[4′,3′,2′:4,5]naphtho[1,2-*d*]-

[1,3]dioxol-5-one (2) and (2aβ,5β,5aα,8aβ,8bβ)-2a,5,5a,6,7,8,8a,8b-Octahydro-5-hydroxy-3,6,6,8b-tetramethyl-2*H*-naphtho[1,8-*bc*]furan-2-one (11). Jones reagent[23] (110 μL) was added dropwise to a stirred solution of **9b** (115 mg, 0.37 mmol) in acetone (4.4 mL) at 0 °C. After complete addition, the mixture was allowed to reach room temperature and stirred until the reaction reached completion as determined by the absence of starting material by TLC (1 h). The reaction was then quenched by the addition of a few drops of 2-propanol and filtered through a Celite pad with copious washings (acetone). The filtrate was neutralized with aqueous $NaHCO_3$ and concentrated, the residue was dissolved in a mixture of H_2O and $CHCl_3$, and the aqueous layer was extracted with $CHCl_3$. The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. The residue was chromatographed to give **9c** (90 mg, 78%) as a solid: mp 164–166 °C; IR ν 1790, 1730, 1385, 1225, 1215, 1180, 1130 cm^{-1}; ^1H NMR δ 4.84 (1 H, dd, J = 2.0 and 6.2 Hz, H-6), 4.28 (1 H, dd, J = 0.8 and 6.2 Hz, H-7), 4.18 (1 H, t, J = 3.6 Hz, H-1), 3.31 (1 H, d, J = 0.8 Hz, H-9), 1.79 (1 H, d, J = 2.0 Hz, H-5), 1.54 (3 H, s), 1.45 (3 H, s), 1.38 (3 H, s), 1.19 (3 H, s), 1.13 (3 H, s); ^{13}C NMR δ 200.08 (C-8), 170.35 (C-11), 111.18 (OCO), 84.67 (C-1), 78.61 (C-6),* 75.03 (C-7)* 66.95 (C-9), 45.14 (C-10), 43.17 (C-5), 35.40 (C-3), 32.87 (C-4), 31.10 (4α-Me), 26.66 (Me, acetonide), 24.75 (Me, acetonide), 22.52 (4β-Me), 21.11 (C-2), 19.90 (10-Me) (the assignments of signals marked with an asterisk (*) may be reversed; mass spectrum, m/e (relative intensity) 308 (M^+, 2), 119 (100).

A solution of β-keto lactone **9c** (62 mg, 0.2 mmol) in anhydrous THF (0.6 mL) was added to a stirred suspension of sodium hydride (5.28 mg, 0.22 mmol) in THF (0.8 mL) at 0 °C. The mixture was kept at 0 °C for 30 min, diethyl phosphorochloridate (38 mg, 0.22 mmol) was then added, and stirring was continued at room temperature. After 2 h, the reaction was quenched by adding solid ammonium chloride (10 mg), and the mixture was filtered through a Celite pad. Concentration of the filtrate afforded a residue (80 mg) that was dissolved in $CHCl_3$. The resulting solution was washed with saturated $NaHCO_3$ solution, dried (Na_2SO_4), and evaporated. The residue (76 mg), by washing with hexane, afforded essentially pure enol phosphate **10**: mp 120.5–121.5 °C; ^1H NMR δ 5.11 (1 H, d, J = 7.5 Hz, H-7), 4.74 (1 H, dd, J = 2.5 and 7.5 Hz, H-6), 4.30 (5 H, m, H-1 and OCH_2CH_3), 1.52 (s), 1.49 (s), 1.36 (t, J = 7.0 Hz, OCH_2CH_3), 1.18 (s), 1.07 (s). This material was used in the next step without further purification.

To a stirred suspension of copper(I) iodide (57 mg, 0.3 mmol) in anhydrous Et_2O (1.5 mL) under argon and at 0 °C was added a 1 M solution of MeLi in Et_2O (Aldrich Chemical Co.) (0.6 mL). The solution was cooled to −78 °C, and the enol phosphate **10** (60 mg, 0.135 mmol) in Et_2O (1.5 mL) was added. The resulting orange mixture was stirred at −78 °C for 3 h, allowed to warm up to −23 °C, and stirred at this temperature until the TLC spot for the starting material had disappeared (4 h). The reaction was then quenched by pouring it into saturated ammonium chloride solution (3 mL), and the aqueous layer was extracted with Et_2O. The combined organic extracts were washed with dilute ammonia and brine, dried (Na_2SO_4), and evaporated. The residue (21 mg) was shown to be a 1:1 mixture of **2** and **11** by NMR analysis. Both products were obtained in pure form by column chromatography: compound **2** (7 mg, 16%): mp 110–111 °C (diisopropyl ether) (lit.[2a,8b] mp 99–100 °C, 110–111 °C, respectively); ^1H NMR δ 4.58 (2 H, m), 4.08 (1 H, m), 2.28 (3 H, s, 8-Me), 1.51 (3 H, s), 1.42 (3 H, s), 1.38 (3 H, s), 1.20 (3 H, s), 1.06 (3 H, s). Compound **11** (8 mg, 22%): mp 144–146 °C (lit.[2a] mp 134–136 °C); IR ν 3483, 1758, 1671, 1175, 972 cm^{-1}; ^1H NMR δ 5.73 (1 H, dt, J = 1.4 and 5.2 Hz, H-7), 4.44 (1 H, br, t, J = 3.5 and 5.2 Hz, H-6), 4.18 (1 H, t, J = 3.5 Hz, H-1), 2.65 (1 H, br s, H-9), 1.96 (3 H, br s, 8-Me), 1.42 (3 H, s), 1.24 (3 H, s), 1.05 (3 H, s); ^{13}C NMR δ 175.74 (C-11), 130.47 (C-8), 126.85 (C-7), 84.02 (C-1), 64.78 (C-6), 58.78 (C-9), 45.59 (C-5), 40.65 (C-10), 36.99 (C-3), 32.47 (C-4), 30.98 (4α-Me), 22.58 (4β-Me), 22.11 (10-Me), 21.36 (C-2), 19.34 (8-Me); mass spectrum, m/e (relative intensity) 250 (M^+, 2), 154 (62), 55 (66), 43 (82), 41 (100). The structures were confirmed by comparing the spectral data for compounds **2** and **11** to the data generously supplied by Professor F. E. Ziegler.

(23) Djerassi, C. D.; Hart, P. A.; Warawa, E. J. *J. Am. Chem. Soc.* **1964**, *86*, 78.

(3aβ,5aβ,6α,6aβ,9aβ,9bα,9cβ)-Decahydro-6-hydroxy-5-methoxy-1,1,8,8,9c-pentamethyl-5*H*-furo[4′,3′,2′:4,5]naphtho[1,2-*d*][1,3]dioxolane (12) and (3aβ,5aβ,6α,6aα,9aα,9bα,9cβ)-Decahydro-6-hydroxy-5-methoxy-1,1,8,8,9c-pentamethyl-5*H*-furo[4′,3′,2′:4,5]naphtho[1,2-*d*][1,3]dioxolane (13). A solution of the crude protected lactol **6b** (529 mg, 2.1 mmol) in CH_2Cl_2 (16 mL) was treated with acetic anhydride (0.9 mL), pyridine (0.525 mL), and a few crystals of 4-(dimethylamino)pyridine. After being stirred at room temperature for 12 h, the mixture was diluted with Et_2O (30 mL) and washed twice with dilute HCl, saturated $NaHCO_3$ solution, and brine. After drying (Na_2SO_4) and removal of the solvent, the residue was chromatographed to give **6d** (400 mg) as a colorless oil: IR (film) ν 1745, 1245, 1115 cm^{-1}; ^1H NMR δ 6.12 (1 H, dd, J = 2.6 and 9.0 Hz, H-6), 5.67 (2 H, m, H-7, H-8), 5.18 (1 H, d, J = 5.6 Hz, H-11), 3.98 (1 H, t, H-1), 3.41 (3 H, s, OCH_3), 2.31 (1 H, dd, J = 5.6 and 9.5 Hz, H-9), 2.30 (1 H, br s, H-5), 2.05 (3 H, s, $OC\text{-}CH_3$), 1.04 (3 H, s), 0.95 (3 H, s), 0.83 (3 H, s); ^{13}C NMR δ 169.95 ($OCCH_3$), 133.34 (C-6), 124.46 (C-7), 106.07 (C-11), 82.21 (C-1), 66.80 (C-8), 57.07 (C-9), 55.80 (OCH_3), 49.00 (C-10), 42.73 (C-5), 34.81 (C-3), 31.44 (4-Me), 31.14 (C-4), 21.84 (C-2), 21.31 (4-Me), 20.62 ($OC\text{-}CH_3$), 17.96 (10-Me); mass spectrum, m/e (relative intensity) 234 (M^+ − 60, 3), 159 (100).

Osmium tetraoxide (513.5 mg, 2.02 mmol) in pyridine (3.4 mL) was slowly added to a stirred solution of acetate **6d** (400 mg, 1.36 mmol) in pyridine (3.4 mL) at 0 °C. The brown solution was kept at 0 °C for 1 h and then warmed to room temperature. After 12 h of stirring in the dark, the osmate ester was reduced by adding THF (20 mL), H_2O (6 mL), Celite (8.12 g), and solid $NaHSO_3$ (2.1 g). The mixture was stirred vigorously at room temperature. When the reaction was complete as judged by TLC (4 h), the mixture was filtered through silica gel with copious washings (EtOAc). Concentration of the filtrate afforded a residue that was dissolved in CH_2Cl_2 (50 mL). The resulting solution was washed with dilute HCl and saturated $NaHCO_3$ solution, dried (Na_2SO_4), and evaporated. The oily residue (438 mg), which was used without further purification, was shown to be a 3:1 mixture of diols, on the basis of its ^1H NMR spectrum. Selected signals of the major isomer in $CDCl_3$–D_2O solution: δ 5.22 (1 H, dd, J = 6.5 and 10.0 Hz, H-8), 4.91 (1 H, d, J = 6.1 Hz, H-11), 4.40 (1 H, br d, J = 3.5 Hz, H-6), 3.79 (1 H, t, H-1), 3.62 (1 H, dd, J = 3.5 and 10.0 Hz, H-7), 3.39 (3 H, s, OCH_3), 2.35 (1 H, dd, J = 6.1 and 6.5 Hz, H-9), the assignments were made on the basis of extensive decoupling experiments.

To a stirred solution of the crude mixture of diols (438 mg) in 2,2-dimethoxypropane (10 mL) was added a crystal of *p*-TsOH at room temperature. After 12 h, the reaction mixture was diluted with Et_2O (50 mL) and washed with saturated $NaHCO_3$ solution and brine. After drying (Na_2SO_4) and removal of the solvent, the residue (486 mg) was dissolved in MeOH (13.6 mL) and treated with K_2CO_3 (560 mg). The mixture was stirred at room temperature for 12 h, after which it was poured into H_2O (30 mL) and extracted with Et_2O (3 × 15 mL) and EtOAc (2 × 10 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. Chromatography of the residue (425 mg) gave, in order of elution, alcohols **12** (107 mg, 25%) and **13** (295 mg, 69%).

Recrystallization of **12** from diisopropyl ether afforded material with a melting point of 157–158 °C: IR ν 3530, 1390, 1230, 1205, 1105, 1020 cm^{-1}; ^1H NMR δ 5.31 (1 H, d, J = 1.93 Hz, H-11), 4.49–4.05 (3 H, m, H-6, H-7, H-8), 3.87 (1 H, t, H-1), 3.37 (3 H, s, OCH_3), 2.35 (1 H, OH), 2.06 (1 H, d, J = 10.3 Hz, H-5), 1.50 (3 H, s), 1.39 (3 H, s), 1.08 (3 H, s), 1.04 (3 H, s), 1.00 (3 H, s); ^{13}C NMR δ 108.05 (OCO), 105.15 (C-11), 81.88 (C-1), 75.34 (C-6),* 73.63 (C-7),* 66.02 (C-8), 59.37 (C-9), 54.75 (OCH_3), 43.60 (C-10), 42.05 (C-5), 34.97 (C-3), 32.34 (4α-Me), 32.02 (C-4), 26.55 (Me, acetonide), 23.82 (Me), 23.66 (Me), 22.80 (Me), 22.64 (C-2) (the assignments for signals marked with an asterisk (*) may be reversed); mass spectrum, m/e (relative intensity) 311 (M^+ − 15, 100), 268 (67). Recrystallization of **13** from diisopropyl ether afforded material with a melting point of 133–134 °C: IR ν 3460, 1380, 1220, 1050, 1005 cm^{-1}; ^1H NMR δ 4.96 (1 H, d, J = 3.95 Hz, H-11), 4.60 (1 H, dd, J = 2.1 and 6.3 Hz, H-6), 4.08 (2 H, m, H-7 and H-8), 3.81 (1 H, t, J = 5.0 Hz, H-1), 3.41 (3 H, s, OCH_3), 2.18 (1 H, dd, J = 3.95 and 5.8 Hz, H-9), 1.64 (1 H, d, J = 2.1 Hz, H-5), 1.50 (3 H, s), 1.40 (3 H, s), 1.35 (3 H, s), 1.09 (3 H, s), 1.02 (3 H,

s); ^{13}C NMR δ 109.54 (OCO), 105.70 (C-11), 84.22 (C-1), 79.39 (C-6),* 73.23 (C-7),* 69.38 (C-8), 58.81 (C-9), 55.29 (OCH_3), 42.99 (C-10), 41.77 (C-5), 35.70 (C-3), 32.52 (C-4), 31.34 (4-Me), 27.40 (Me, acetonide), 24.80 (Me), 24.50 (Me), 22.98 (10-Me), 22.47 (C-2) (the assignments for signals marked with an asterisk (*) may be reversed); mass spectrum, m/e (relative intensity) 326 (M^+, 3), 166 (100). Anal. Calcd for $C_{18}H_{30}O_5$: C, 66.23; H, 9.26. Found: C, 66.14; H, 9.03.

(3aβ,6aα,9aα,9bα,9cβ)-1,2,3,3a,6a,9a,9b,9c-Octahydro-1,1,6,8,8,9c-hexamethyl-5*H*-furo[4',3',2':4,5]naphtho[1,2-*d*]-[1,3]dioxol-5-one (2). To a stirred solution of alcohol **13** (62 mg, 0.19 mmol) in CH_2Cl_2 (5.7 mL) redistilled over pyridinium dichromate (PDC)[24] was added finely powdered PDC (120 mg, 0.32 mmol) and acetic acid (21 μL), and the resulting mixture was stirred at room temperature. After 4 h, Celite (100 mg) was added, and the mixture was stirred for further 20 min and filtered through silica gel with copious washings (EtOAc). Concentration and chromatography of the residue gave ketone **14** (61 mg, 99%): mp 115.5–116 °C; IR ν 1740, 1405, 1390, 1220, 1120, 1110, 1075, 1060, 1050 cm^{-1}; ^1H NMR δ 5.13 (1 H, d, J = 2.0 Hz, H-11), 4.80 (1 H, dd, J = 1.74 and 8.0 Hz, H-6), 4.18 (1 H, d, J = 8.0 Hz, H-7), 3.76 (1 H, t, J = 5.0 Hz, H-1), 3.29 (3 H, s, OCH_3), 2.85 (1 H, d, J = 2.0 Hz, H-9), 1.53 (3 H, s), 1.51 (3 H, s), 1.28 (3 H, s), 1.06 (3 H, s), 0.95 (3 H, s); ^{13}C NMR δ 206.16 (C-8), 111.64 (OCO), 104.94 (C-11), 84.56 (C-1), 78.51 (C-7), 76.63 (C-6), 66.49 (C-9),54.92 (OCH_3), 46.28 (C-10), 45.16 (C-5), 35.24 (C-3), 32.83 (C-4), 30.95 (4α-Me), 25.54 (Me), 24.36 (Me), 24.14 (Me), 23.44 (Me), 22.48 (C-2); mass spectrum, m/e (relative intensity) 323 ($M^+ - 1$, 2), 266 (100).

Preparation of 15a. Method A. A solution of the ketone **14** (102.7 mg 0.32 mmol) in anhydrous Et_2O (3 mL) was added slowly to a stirred solution of methylmagnesium iodide (2.6 mmol) in anhydrous Et_2O (5 mL) at 0 °C, and the resulting solution was allowed to warm to room temperature. After 1 h the reaction was quenched by the careful addition of saturated ammonium chloride solution and extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated to afford **15a** (107 mg, 99%), which was homogeneous by NMR analysis: IR ν 3490, 1390, 1280, 1220, 1110, 1070 cm^{-1}; ^1H NMR δ 5.01 (1 H, s, H-11), 4.61 (1 H, dd, J = 2.0 and 8.0 Hz, H-6), 3.95 (1 H, d, J = 8.0 Hz, H-7), 3.77 (1 H, t, H-1), 3.34 (3 H, s, OCH_3), 2.00 (1 H, s, H-9), 1.92 (1 H, d, J = 2.0 Hz, H-5), 1.46 (3 H, s), 1.44 (3 H, s), 1.36 (3 H, s), 1.32 (3 H, s), 1.10 (3 H, s), 1.01 (3 H, s); ^{13}C NMR δ 107.70 (OCO), 106.20 (C-11), 85.68 (C-1), 80.07 (C-6),* 72.78 (C-7),* 70.12 (C-8), 59.95 (C-9), 54.05 (OCH_3), 41.88 (C-10), 39.44 (C-5), 34.66 (C-3), 31.88 (C-4), 30.38 (4α-Me), 27.76 (Me), 26.70 (Me), 25.60 (Me), 23.76 (C-2), 22.76 (10-Me) (the assignments for signals marked with an asterisk (*) may be reversed). This material was used in the next step without further purification.

Method B. To a stirred solution of MeLi (Aldrich Chemical Co.) (0.35 mL of 1.3 M solution in Et_2O, 0.45 mmol) in anhydrous Et_2O (1.0 mL) under argon and at −80 °C was added a solution of **14** (44 mg, 0.14 mmol) in anhydrous Et_2O (1.6 mL). After being stirred for 30 min at −80 °C, the solution was warmed up to room temperature and stirred for a further 30 min. The reaction was then quenched by the careful addition of saturated ammonium chloride solution and extracted with Et_2O (2 × 5 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. The residue was chromatographed to give pure **15a** (14 mg, 30%), identical with the product obtained by the addition of methylmagnesium iodide to **14** (TLC, ^1H NMR).

Jones reagent (226 μL) was added dropwise to a stirred solution of **15a** (107 mg, 0.31 mmol), in acetone (14 mL) at 0 °C. After complete addition of the oxidizing agent, the mixture was allowed to reach room temperature and stirred until the reaction reached completion as determined by the absence of starting material by TLC (1 h). The reaction was then quenched by the addition of a few drops of 2-propanol. Celite (200 mg) was added, and the mixture was filtered through silica gel with copious washings (EtOAc). The filtrate was concentrated, and the residue chromatographed to yield lactone **15b** (100.9 mg, 82%): mp 153–154 °C; IR ν 3440, 1750, 1400, 1380, 1280, 1225, 1070, 1050 cm^{-1}; ^1H NMR δ 4.70 (1 H, dd, J = 2.9 and 8.0 Hz, H-6), 4.18 (1 H, d, J = 8.0 Hz, H-7), 4.04 (1 H, t, J = 5.0 Hz, H-1), 2.93 (1 H, s, OH), 2.51 (1 H, s, H-9), 1.78 (1 H, d, J = 2.9 Hz, H-5), 1.59 (3 H, s), 1.50 (3 H, s), 1.36 (3 H, s), 1.14 (3 H, s), 1.07 (3 H, s); ^{13}C NMR δ 178.17 (C-11), 108.18 (OCO), 86.61 (C-1), 79.88 (C-6),* 72.04 (C-7),* 69.06 (C-8), 59.72 (C-9), 40.29 (C-5), 40.03 (C-10), 35.64 (C-3), 32.19 (C-4), 30.88 (4α-Me), 29.06 (Me), 25.14 (Me), 25.04 (Me), 23.94 (Me), 22.89 (10-Me), 22.18 (C-2) (the assignments for signals marked with an asterisk (*) may be reversed); mass spectrum, m/e (relative intensity) 324 (M^+, 100), 309 (76), 249 (97), 231 (58); found for M^+ m/e 324.1942 ($C_{18}H_{28}O_5$ requires m/e 324.1937).

Freshly distilled thionyl chloride (0.2 mL) was added to a stirred solution of **15b** (67.3 mg, 0.21 mmol) in pyridine (1 mL) in an ice bath. After 1 h at this temperature, the starting material was consumed and a less polar product was formed as judged by TLC. The mixture was diluted with CH_2Cl_2 (20 mL), and the resulting solution was successively washed with cold 5% aqueous HCl (2 × 5 mL), saturated $NaHCO_3$ solution, and brine, dried (Na_2SO_4), and evaporated. The residue (63 mg, 100%), which crystallized on standing, was shown to be a 10:1 mixture of **2** and **16** by NMR analysis: ^1H NMR δ 5.68 (s), 5.49 (s), 4.08 (m), 3.08 (s), 2.28 (s), 1.51 (s), 1.42 (s), 1.39 (s), 1.20 (s), 1.06 (s). The ratio of both components was estimated by comparing the areas under the signals at δ 5.68, 5.49 and 3.08, unequivocally assigned to the exocyclic methylene and H-9 of **16**, with that of the vinylic methyl of **2** at δ 2.28. Slow crystallization of the crude product from diisopropyl ether provided pure **2**: mp 110–111 °C (lit.[2a,8b] mp 99–100 °C, 110–111 °C, respectively; IR ν 1750, 1680, 1385, 1215, 1200, 1050, 1040, 1025 cm^{-1}; ^1H NMR 4.58 (2 H, m, H-6, H-7), 4.08 (1 H, m, H-1), 2.28 (3 H, s, 8-Me), 1.51 (3 H, s), 1.42 (3 H, s), 1.38 (3 H, s), 1.20 (3 H, s), 1.06 (3 H, s); ^{13}C NMR δ 169.03 (C-11), 144.44 (C-8), 136.56 (C-9), 109.09 (OCO), 87.34 (C-1), 79.21 (C-6),* 73.05 (C-7),* 51.49 (C-5), 40.28 (C-10), 36.04 (C-3), 32.10 (C-4), 30.94 (Me), 28.17 (Me), 26.15 (Me × 2), 24.99 (C-2), 22.76 (Me), 17.67 (Me) (the assignments for signals marked with an asterisk (*) may be reversed); mass spectrum, m/e (relative intensity) 306 (M^+, 46), 291 (41), 43 (100); found for M^+ m/e 306.1832 ($C_{18}H_{26}O_4$ requires 306.1831).

(3aβ,5aβ,6aα,9aα,9bα,9cβ)-Decahydro-1,1,8,8,9c-pentamethyl-6-methylene-5*H*-furo[4',3',2':4,5]naphtho[1,2-*d*]-[1,3]dioxol-5-one (16). To a magnetically stirred suspension of methyltriphenylphosphonium bromide (120 mg, 0.33 mmol) in dry THF (1 mL) was added a 2.2 M solution of *n*-BuLi in hexane (0.29 mL), and the resulting solution was stirred at room temperature for 20 min. To this solution was added the ketone **14** (30 mg, 0.09 mmol) in THF (1 mL). After 3 h of stirring at room temperature, the reaction mixture was poured into H_2O (15 mL) and extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. The residue was chromatographed to give **17** (17 mg, 57%) as a solid: IR ν 1645, 1470, 1460, 1390, 1380, 1220, 1040 cm^{-1}; ^1H NMR δ 5.40 (1 H, t, J = 1.4 Hz, C=CH_2), 5.24 (1 H, t, J = 1.6 Hz, C=CH_2), 4.83 (1 H, d, J = 3.95 Hz, H-11), 4.60 (2 H, br s, H-6 and H-7), 3.79 (1 H, t, J = 3.5 Hz, H-1), 3.40 (3 H, s, OCH_3), 2.65 (1 H, m, H-9), 1.50 (3 H, s), 1.37 (6 H, s), 1.12 (3 H, s), 1.02 (3 H, s); ^{13}C NMR δ 141.89 (C-8), 119.04 (C=CH_2), 109.53 (C-11), 108.99 (OCO), 84.34 (C-1), 77.91 (C-6),* 73.92 (C-7),* 61.59 (C-9), 55.59 (OCH_3), 44.48 (C-5), 43.15 (C-10), 36.35 (C-3), 33.11 (C-4), 31.51 (4α-Me), 26.20 (Me), 24.13 (Me), 23.28 (Me), 22.05 (C-2), 21.68 (10-Me) (the assignments for signals marked with an asterisk (*) may be reversed). This material was used in the next step without further purification.

Jones reagent (75 μL) was added dropwise to a stirred solution of **17** (37 mg, 0.11 mmol) in acetone (4.8 mL) at 0 °C. After complete addition of the oxidizing agent, the mixture was allowed to reach room temperature and stirred for 3 h, Jones reagent was again added (75 μL), and the stirring was continued for a further 4 h at room temperature. The reaction was then quenched by the addition of a few drops of 2-propanol. Celite (400 mg) was added; the mixture was stirred for an additional 0.5 h and filtered through silica gel with copious washings (EtOAc). The filtrate was concentrated, and the residue upon chromatographic purification gave starting material **17** (11 mg, 30%) and lactone **16** (12 mg, 35%): mp 143–144 °C; IR ν 1770, 1640, 1380, 1260, 1210, 1030, 900 cm^{-1}; ^1H NMR δ 5.68 (1 H, br s, C=CH_2), 5.49 (1 H,

(24) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.

br s, C=CH_2), 4.58 (2 H, m, H-6, H-7), 4.10 (1 H, t, H-1), 3.08 (1 H, br s, H-9), 1.52 (1 H, br s, H-5), 1.48 (6 H, s) 1.36 (3 H, s), 1.16 (3 H, s), 1.05 (3 H, s); ^{13}C NMR δ 175.80 (C-11), 136.31 (C-8), 123.03 (C=CH_2), 109.69 (OCO), 84.34 (C-1), 76.31 (C-6),* 72.97 (C-7),* 59.52 (C-9), 44.00, 41.77, 36.03, 32.89, 31.19, 26.84, 24.76, 22.42, 21.42, 20.25 (the assignments for signals marked with an asterisk (*) may be reversed); found for $M^+ - 15$ m/e 291.1585 ($C_{17}H_{23}O_4$ requires 291.1596).

The structure was confirmed by comparing the ^{1}H NMR spectral data for compound **16** to the data generously supplied by Professor F. E. Ziegler.

(3aβ,5aβ,6aβ,9aβ,9bα,9cβ)-Decahydro-5-methoxy-1,1,8,8,9c-pentamethyl-5*H*-furo[4′,3′,2′:4,5]naphtho[1,2-*d*]-[1,3]dioxol-6-one (23). To a stirred solution of alcohol **12** (47.6 mg, 0.15 mmol) in CH_2Cl_2 (4.5 mL), redistilled over pyridinium dichromate (PDC), were added finely powdered PDC (94.6 mg, 0.25 mmol) and acetic acid (16 μL), and the resulting mixture was stirred at room temperature. After 31 h, Celite (80 mg) was added, and the mixture was stirred for further 20 min and filtered through silica gel with copious washings (EtOAc). Concentration of the filtrate afforded a residue that crystallized on standing (43 mg, 91%). Recrystallization of **23** from diisopropyl ether afforded material with a melting point of 141–142 °C: IR ν 1740, 1385, 1375, 1225, 1100, 1025 cm^{-1}; ^{1}H NMR (500 MHz) δ 5.20 (1 H, d, J = 2.6 Hz, H-11), 4.70 (2 H, m, H-6, H-7), 3.92 (1 H, t, J = 3.0 Hz, H-1), 3.40 (3 H, s, OCH_3), 2.49 (1 H, d, J = 2.6 Hz, H-9), 1.85 (2 H, m), 1.49 (3 H, s), 1.38 (6 H, s), 1.24 (2 H, m), 1.17 (1 H, d, J = 9.5 Hz, H-5), 1.03 (3 H, s), 0.99 (3 H, s); ^{13}C NMR δ 205.3 (C-8), 110.7 (OCO), 104.1 (C-11), 81.6 (C-1), 78.7 (C-6),* 77.0 (C-7),* 68.9 (C-9), 55.05 (OCH_3), 48.8 (C-5), 45.3 (C-10), 34.8 (C-3), 32.6 (C-4), 32.6 (Me), 27.1 (Me), 25.3 (Me), 21.26 (Me), 21.10 (C-2), 21.04 (Me) (the assignments for signals marked with an asterisk (*) may be reversed); mass spectrum, m/e (relative intensity) 324 (M^+, 2), 189 (24), 149 (26), 43 (100); found for M^+ m/e 324.1893 ($C_{18}H_{28}O_5$ requires 324.1937). Anal. Calcd for $C_{18}H_{28}O_5$: C, 66.64; H, 8.70. Found: C, 66.79; H, 8.75.

(3aβ,6aβ,9aβ,9bα,9cβ)-1,2,3,3a,6a,9a,9b,9c-Octahydro-1,1,6,8,8,9c-hexamethyl-5*H*-furo[4′,3′,2′:4,5]naphtho[1,2-*d*]-[1,3]dioxol-5-one (18). To a stirred solution of MeLi (1.4 mL of 0.8 M solution in Et_2O), prepared according to ref 25, in anhydrous Et_2O (2.3 mL) at 0 °C, was added a solution of **23** (80.1 mg, 0.2 mmol) in anhydrous Et_2O (4.3 mL). After the mixture was stirred for 15 min at 0 °C, the reaction was quenched by the careful addition of saturated ammonium chloride solution and extracted with Et_2O (2 × 15 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. The residue (80 mg) was chromatographed to give pure **24a** (59.4 mg, 71%): mp 116–118 °C; IR ν 3540, 1395, 1225, 1110, 1055 cm^{-1}; ^{1}H NMR δ 5.28 (1 H, d, J = 2.1 Hz, H-11), 4.36 (1 H, dd, J = 7.5 and 10.5 Hz, H-6), 3.95 (1 H, d, J = 7.5 Hz, H-7), 3.83 (1 H, t, J = 5.0 Hz, H-1), 3.37 (3 H, s, OCH_3), 2.12 (1 H, d, J = 10.5 Hz, H-5), 1.67 (1 H, d, J = 2.1 Hz, H-9), 1.48 (3 H, s), 1.37 (3 H, s), 1.26 (3 H, s), 1.07 (3 H, s), 1.01 (3 H, s), 0.98 (3 H, s); ^{13}C NMR δ 108.14 (OCO), 105.28 (C-11), 81.84 (C-1), 79.29 (C-6),* 74.29 (C-7),* 70.04 (C-8), 64.99 (C-9), 54.89 (OCH_3), 44.11 (C-10), 41.88 (C-5), 35.22 (C-3), 32.47 (Me), 32.09 (C-4), 29.12 (Me), 26.73 (Me), 23.91 (Me), 23.65 (Me), 22.62 (Me), 22.53 (C-2); (the assignments for signals marked with an asterisk (*) may be reversed).

Jones reagent (94.4 μL) was added dropwise to a stirred solution of **24a** (44 mg, 0.13 mmol) in acetone (6.1 mL) at 0 °C. After complete addition, the mixture was allowed to reach room temperature and stirred until the reaction reached completion as determined by the absence of starting material by TLC (45 min). The reaction was then quenched by the addition of a few drops of 2-propanol, Celite (100 mg) was added, and the mixture was filtered through silica gel with copious washings (EtOAc). Concentration of the filtrate afforded **24b** as a residue (40 mg) that crystallized on standing: IR ν 3520, 1755, 1375, 1215 cm^{-1}; ^{1}H NMR δ 4.41 (1 H, d, J = 7.1 and 10.0 Hz, H-6), 4.07 (1 H, t, J = 5.7 Hz, H-1), 3.96 (1 H, d, J = 7.1 Hz, H-7), 2.29 (1 H, d, J = 10.0 Hz, H-5), 2.27 (1 H, s, H-9), 1.54 (3 H, s), 1.51 (3 H, s), 1.40 (3 H, s), 1.20 (3 H, s), 1.08 (3 H, s), 1.05 (3 H, s); ^{13}C NMR δ 174.61 (C-11), 109.12 (OCO), 83.28 (C-1), 79.19 (C-6),* 73.64 (C-7),* 70.38 (C-8), 59.09 (C-9), 41.60 (C-10), 41.51 (C-5), 33.98 (C-3), 31.83 (4α-Me), 31.37 (C-4), 27.79 (Me), 26.46 (Me), 24.71 (Me), 24.39 (Me), 23.20 (Me), 22.83 (C-2) (the assignments for signals marked with an asterisk (*) be reversed). This material was used in the next step without further purification.

A well-stirred mixture of **24b** (30 mg, 0.09 mmol) in dioxane (2 mL) containing solid potassium hydroxide (180 mg) was heated at 85 °C, and the reaction was monitored by TLC. After approximately 8 h, TLC indicated the formation of a polar material and the total consumption of the starting material. The mixture was cooled, poured into H_2O, acidified by the addition of 5% aqueous HCl, and extracted with CH_2Cl_2 (2 × 15 mL). The combined organic extracts were washed with brine, dried, and evaporated. The residue (22.7 mg, 80%) crystallized on standing. Recrystallization of **18** from diisopropyl ether afforded material with a melting point of 134–135 °C: IR ν 1750, 1680, 1390, 1220, 1030 cm^{-1}; ^{1}H NMR (500 MHz) δ 4.78 (1 H, dd, J = 1.3 and 8.0 Hz, H-7), 4.67 (1 H, dd, J = 8.0 and 10.0 Hz, H-6), 4.10 (1 H, dd, J = 6.7 and 11.0 Hz, H-1), 2.24 (1 H, d, J = 1.3 Hz, 8-Me), 1.34 (1 H, d, J = 10.0 Hz, H-5), 1.42 (6 H, s), 1.11 (6 H, s), 1.08 (3 H, s); ^{13}C NMR δ 168.20 (C-11), 148.27 (C-8), 131.74 (C-9), 109.69 (OCO), 85.14 (C-1), 76.63 (C-6),* 74.40 (C-7),* 48.68 (C-5), 41.93 (C-10), 35.39 (C-3), 31.41 (4α-Me), 31.14 (C-4), 26.84 (Me), 25.45 (Me), 24.55 (C-2), 24.07 (Me), 23.12 (Me), 13.13 (Me) (the assignments of signals marked with an asterisk (*) may be reversed); mass spectrum, m/e (relative intensity) 306 (M^+, 35), 291 (41), 248 (65), 43 (100); high-resolution mass spectrum (CI, NH_3) calcd for $C_{18}H_{27}O_4$ $(M + H)^+$ m/e 307.1909, found m/e 307.1941. Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.84; H, 8.55.

(3aβ,5aβ,6aβ,9aβ,9bα,9cβ)-Decahydro-5-methoxy-1,1,8,8,9c-pentamethyl-5*H*-furo[4′,3′,2′:4,5]naphtho[1,2-*d*]-[1,3]dioxol-6-one (23). To a stirred solution of methyl acetal **6b** (154 mg, 0.61 mmol) in CH_2Cl_2 (18 mL) redistilled over pyridinium dichromate (PDC) was added finely powdered PDC (377 mg, 1.00 mmol) and acetic acid (66 μL), and the resulting mixture was stirred at room temperature. After 4 h, Celite (100 mg) was added, and the mixture was stirred for a further 20 min and filtered through silica gel with copious washings (EtOAc). Concentration and chromatography of the residue gave ketone **27** (121.6 mg, 80%): mp 74–76 °C; IR ν 1680, 1600, 1380, 1250, 1100, 1020, 970 cm^{-1}; ^{1}H NMR δ 7.06 (1 H, dd, J = 3.2 and 10.0 Hz, H-6), 6.05 (1 H, dd, J = 3.2 and 10.0 Hz, H-7), 5.01 (1 H, d, J = 4.6 Hz, H-11), 3.99 (1 H, t, J = 3.2 Hz, H-1), 3.44 (3 H, s, OCH_3), 2.52 (1 H, d, J = 4.6 Hz, H-9), 2.46 (1 H, t, J = 3.1 Hz, H-5), 1.18 (3 H, s), 1.00 (3 H, s), 0.98 (3 H, s); ^{13}C NMR δ 196.33 (C-8), 150.44 (C-6), 129.03 (C-7), 104.89 (C-11), 80.71 (C-1), 68.87 (C-9), 55.62 (OCH_3), 49.19 (C-10), 44.91 (C-5), 34.44 (C-3), 31.44 (Me), 31.20 (C-4), 21.25 (C-2), 21.25 (Me), 18.15 (Me); mass spectrum, m/e (relative intensity) 250 (M^+, 1), 134 (100).

Osmium tetraoxide (202 mg, 0.79 mmol) in pyridine (1.3 mL) was slowly added to a stirred solution of ketone **27** (177.5 mg, 0.71 mmol) in pyridine (1.8 mL) at 0 °C. The brown solution was kept at 0 °C for 1 h and then warmed to room temperature. After 6 h of stirring in the dark, the osmate ester was reduced by adding THF (10.6 mL), H_2O (3.17 mL), Celite (4.23 g), and solid $NaHSO_3$ (1.065 g). The mixture was stirred vigorously at room temperature. When the reaction was complete as judged by TLC (19 h), the mixture was filtered through silica gel with copious washings (EtOAc). Concentration of the filtrate afforded a residue that was dissolved in CH_2Cl_2 (30 mL). The resulting solution was washed with dilute HCl and saturated $NaHCO_3$ solution, dried (Na_2SO_4), and evaporated. The residue (195.7 mg) that crystallized on standing, was used in the next step without further purification.

To a solution of the crude mixture of diols in 2,2-dimethoxypropane (3 mL) was added a crystal of p-TsOH at room temperature. After 16 h, the reaction mixture was diluted with Et_2O (25 mL) and washed with saturated $NaHCO_3$ solution and brine, dried (Na_2SO_4), and evaporated. Chromatography of the residue (221.7 mg) gave, in order of elution, ketones **14** (21.4 mg, 9%) and **23** (163.4 mg, 71%), identical with the products obtained by oxidation of alcohols **13** and **12**, respectively (TLC, ^{1}H NMR).

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Supplementary Material Available: ^1H and ^{13}C NMR spectra for compounds **6b,d**, **8a,b**, **9a–c**, **10**, **12–14**, **15a,b**, **16–18**, **23**, **24a,b**, **26**, and **27** (62 pages). Ordering information is given on any current masthead page.

Selective Functionalization of Calix[4]arenes at the Upper Rim

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Methods are described for the selective diametrical functionalization of calix[4]arenes at the upper rim, either by the selective removal of the *p-tert*-butyl groups and subsequent substitution at the free phenol rings or by selective reactions at the phenol rings of dialkoxycalix[4]arenes without the *tert*-butyl groups. This includes selective mercuration and the synthesis of 5,17-di-*tert*-butyl-26,28-dimethoxy-11,23-diphenylcalix[4]arene (**13**), of which the crystal structure is described. The first synthesis of macrocyclic diquinones derived from calix[4]arenes (calix[4]diquinones) is described.

The interest in calix[4]arene chemistry is rapidly increasing because its derivatives can form inclusion complexes with cations or with neutral molecules.[1] The parent *p-tert*-butylcalix[4]arene (**1**)[2] contains two interesting substructures. At the lower rim[1] four hydroxyl groups are present in very close proximity; these can be used for cation binding[3] and transport.[4] The upper rim contains a hydrophobic cavity that is potentially able to complex neutral substrates. The introduction of ester, keto, or amide groups at the lower rim of **1** fixes this macrocycle in a cone conformation, giving *sodium*-selective cation ligands.[5] We have recently bridged the lower rim of *p-tert*-butylcalix[4]arene (**1**) for the synthesis of a new class of *potassium*-selective cation receptors, the calixspherands and the calixcrowns.[6] The calixspherands are able to form *kinetically* stable complexes with Na^+, K^+, and Rb^+.

Surprisingly, only a limited number of complexes are described with hydrophobic organic substrates complexed in the *upper rim* cavity. Except for some complexes in the solid state,[7] and the complexes in water based on hydrophobic or electrostatic forces,[8] only several amines are known to form a complex in the upper rim cavity in solution.[9] The reason is the lack of appropriate functionalization at the upper rim.

The cavity of the upper rim can be modified by introducing substituents at the para positions of the phenol rings of calix[4]arene (**2**). Gutsche et al. have described modification via a Claisen rearrangement[10] and via an intermediate *p*-quinone methide.[11] Shinkai et al. succeeded in sulfonation and nitration,[12] and we have performed the chloromethylation.[13] However, these methods only give access to *tetra*substituted calix[4]arenes with four identical substituents at the para positions of the phenol rings. In principle it would be desirable to have individual control of the para substitution of the four aromatic rings, but except for one example by Gutsche and Lin,[14] until now the only method to obtain nonsymmetrically substituted calix[4]arenes are the stepwise routes developed by Böhmer et al.[15] Therefore we are currently investigating

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